COMMONWEALTH OF AUSTRALIA

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Warning

CHARLES DARWIN UNIVERSITY

Family Name	
Given Names	
Student Number	
Teaching Period	Semester 1, 2016

FINAL EXAMINATION	**DURATION**
PHA212 – Medicinal Chemistry	Reading Time: **10** minutes Writing Time: **180** minutes

INSTRUCTIONS TO CANDIDATES

Section A

Short Answer Questions

Total No of Marks for this section: 100

This section should be answered in the Answer Booklet provided.

Marks for each question are indicated. Suggested Time allocation for Section A: 180 mins

EXAM CONDITIONS

You may begin writing from the commencement of the examination session. The reading time indicated above is provided as a guide only.

This is a CLOSED BOOK examination

Any non-programmable calculator is permitted

No handwritten notes are permitted

No dictionaries are permitted

ADDITIONAL AUTHORISED MATERIALS	EXAMINATION MATERIALS TO BE SUPPLIED
No additional printed material is permitted	1 x 20 Page Book 1 x Scrap Paper

THIS EXAMINATION IS PRINTED DOUBLE-SIDED.

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Section A

Short Answer Questions

Total No of Marks for this section: 100

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Question 1. Drug development process and methods

(a) As chief scientific officer of a medium sized biopharma company specialising in oncology, you have been asked for you opinion on whether your company should buy the intellectual property relating to a new cancer chemotherapeutic from a university start-up. The project is targeting what is believed to be a novel mechanism for disrupting mitosis. The project has progressed to the stage of having several hits in a biophysical screening campaign.

What information would you expect the start-up to provide as part of the IP? Produce an annotated schematic that you could use as part of your briefing to the company board explaining the benefits and risks associated with taking on this project. Assume that the annotations need to be sufficient for the schematic to be understood without you being present to explain it.

(Marks 10)

(b) Tropical diseases affect more than 1 billion people, mostly in developing regions of the world.

i. Give 2 examples of tropical diseases.

ii. Give four parameters for developing drugs targeting **neglected** tropical diseases and explain their importance

(Marks 10)

Question 2. Metabolomics and natural regulators

(a) Natural regulators are common starting points for new drugs. Explain, including diagrams and/or examples, why many natural regulators, particularly neurotransmitters and peptide hormones are not good candidates for direct use as pharmaceuticals and thus require the application of medicinal chemistry to turn them into marketable drugs. Factors you should consider are:

- Stability
- Structural rigidity
- Lipophilicity
- Polarity
- Unsuitable functional groups

(Marks 10)

(b) In one sentence define the following terms:

i. Metabolomics

ii. Lipidomics

iii. Metabolic footprinting

(Marks 3)

(c) Using a flowchart, outline the key steps in the metabolomics analysis (profiling) of tissue extracts taken from a study of 50 individuals. Include details on sample preparation and the suggested analytical platform to be used (note separation and detection method)

(Marks 7)

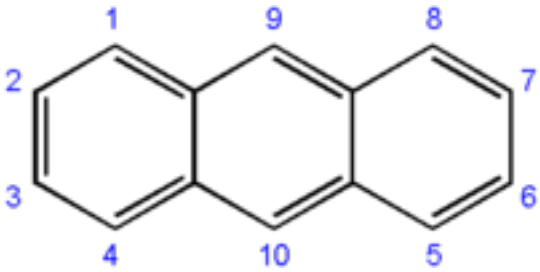
Question 3. Hit-to-lead chemistry

(a) Define:

i. Homologous series
ii. Pro-drug
iii. Log P
iv. The "rule of five" (2 marks)

(Marks 5)

(b) Describe the chemical and structural and potential binding effects making changes to the size, bonding and atoms in the central ring (carbons numbered 9 and 10) of the following compound (anthracene):

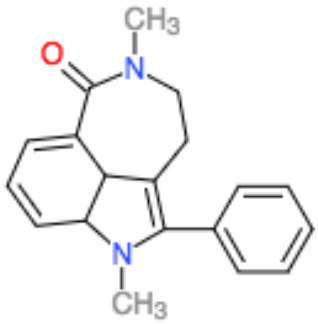


Factors to consider are:

- non-aromatic carbons
- change to seven membered ring
- introduction of heteroatoms at positions 9 and 10
- combination of heteroatoms and seven membered ring

(Marks 8)

(c) The compound below was discovered to be an effective enzyme inhibitor. What modifications would you make to this compound in order to discover the pharmacophore and which groups may be interfering with target binding?



(Marks 7)

Question 4. Screening and structure based design

(a) Define:

i. Allosteric inhibitor
ii. Antagonist
iii. Pharmacophore
iv. Phenotypic screening

(Marks 4)

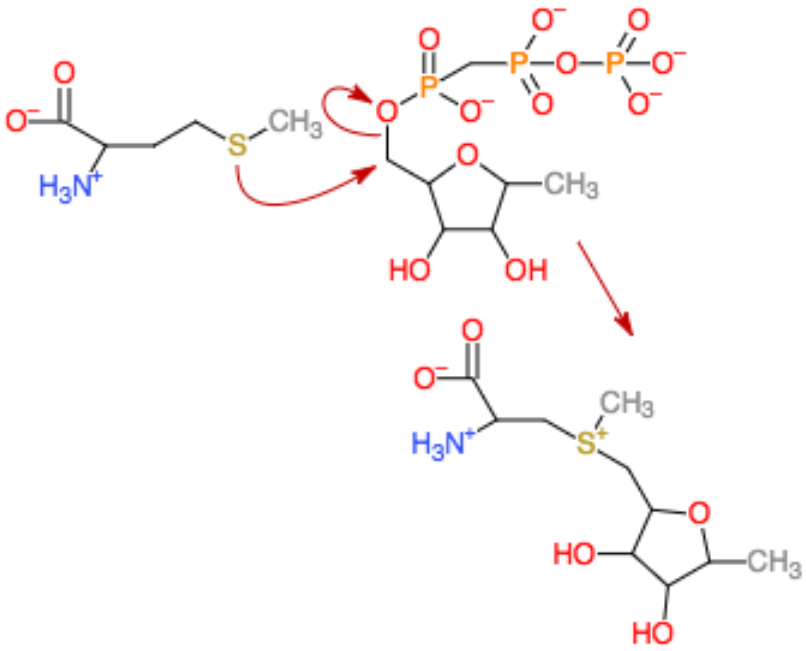
(b)

i. In the diagram below, what type of reaction is occurring?

Using the concept of bioisosteres:

ii. Design a reversible competitive inhibitor for the following reaction. Explain your reasoning

iii. Design a multi-substrate analogue inhibitor. Explain your reasoning



(Marks 7)

(c) Surface plasmon resonance, isothermal titration calorimetry and nuclear magnetic resonance are all common biophysical methods for screening compound libraries for binding to isolated target molecules.

In terms of structural information gathered, binding kinetics and thermodynamics, explain the relative advantages of these three techniques for screening a pharmaceutical compound library for binding to a soluble protein target.

(Marks 9)

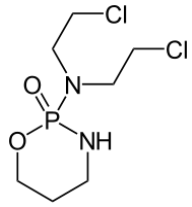
Question 5. Drug-target interaction chemistry

(a) Explain and give examples of the following types of chemical interaction:

i. Van der Waals forces
ii. Dipole-ion interaction
iii. Hydrogen bonding

(Marks 6)

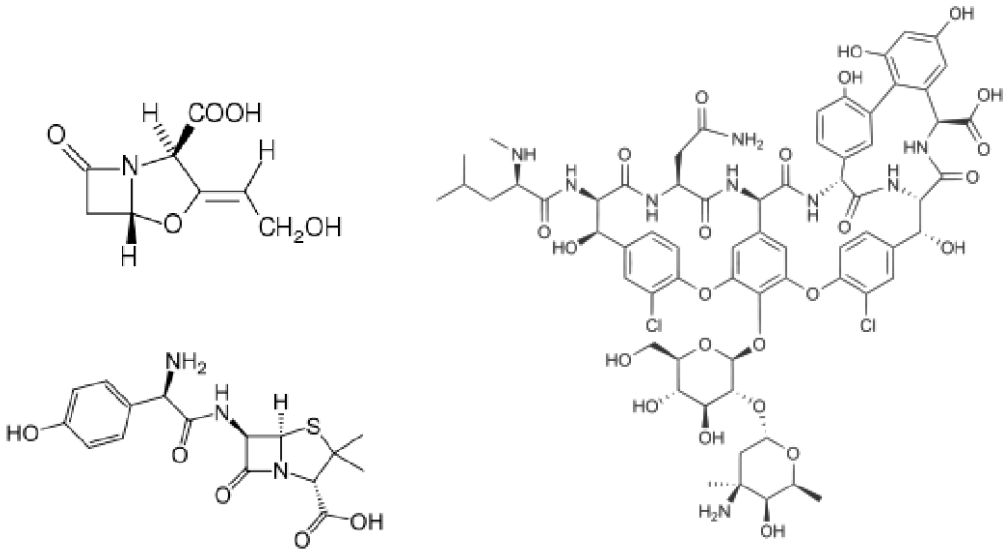
(b) Draw, annotate and explain the organic chemical reaction mechanism for the interaction between alkylating cytotoxic cancer chemotherapeutic cyclophosphamide (structure below) and DNA



(Marks 6)

(c) Beta-lactams (e.g. amoxicillin) and glycopeptide antibiotics (e.g. vancomycin) both inhibit the enzyme responsible for building bacterial cell walls (D-D-transpepidases).

i. Explain the chemical reasons (including mechanisms if needed) that amoxicillin is orally bioavailable while vancomycin is not
ii. Explain the chemical reasons (including mechanisms if needed) that amoxicillin is often given in conjunction with clavulanic acid but is not used in vancomycin treatment



(Marks 8)